Clinical Medicine & Research
Volume 5, Number 4: 228-237

http://www.clinmedres.org

Review

Tumor-Related Hyponatremia

Adedayo A. Onitilo, MD, MSCR, FACP; Ebenezer Kio, MD; and Suhail A. R. Doi, MBBS, FRCP, PhD

Hyponatremia is an important and common electrolyte disorder in tumor patients and one that has been reported in association with a number of different primary diagnoses. The correct diagnosis of the pathophysiological basis for each patient is important because it significantly alters the treatment approach. In this article, we review the epidemiology and presentation of patients with hyponatremia, the pathophysiologic groups for the disorder with respect to sodium and water balance and the diagnostic measures for determining the correct pathophysiologic groups. We then present the various treatment options based on the pathophysiologic groups including a mathematical approach to the use of hypertonic saline in management. In cancer patients, hyponatremia is a serious co-morbidity that requires particular attention as its treatment varies by pathophysiologic groups, and its consequences can have a deleterious effect on the patient's health.

Keywords: Antidiuretic hormone; Arginine vasopressin; Cancer; Hypertonic saline; Hyponatremia; Malignancy; SIADH; Sodium

Hyponatremia, a serious electrolyte disorder associated with life-threatening neurological complications, is one of the most common electrolyte disorders associated with tumor-related conditions.[1] Mild hyponatremia is defined as a serum sodium concentration <135, moderate <132, severe <130 mmol/L and life threatening <125 or abnormal sodium concentration with clinical signs.[2] It usually accompanies, but can also precede the diagnosis of the tumor with an incidence of about 3.7% to 5%[3] and may result from medical[4] or surgical intervention.[5] Hyponatremia develops most often when the ability of the kidney to excrete free water is impaired; hence it is primarily a disorder of water metabolism without impact on intravascular volume status.[6] However, when the former is associated with loss or gain of total body sodium, features of changes in intravascular volume are also associated.[6]

This review focuses on hyponatremia in tumor-related conditions and tries to provide a state-of-the-art understanding of presentation, management and outcome.

PATHOPHYSIOLOGY OF HYPONATREMIA

Dehydration or overhydration largely refers to intracellular water deficits or excesses stemming from hypertonicity or hypotonicity mediated via a disturbance in water metabolism.[7] The diagnosis of dehydration or overhydration cannot be established without laboratory analysis of serum sodium (high or low, respectively) or calculation of serum tonicity (high or low, respectively).[7] In contrast, volume depletion describes the net loss of total body sodium and a reduction in intravascular volume and is best termed extracellular fluid volume depletion. It is mediated via changes in sodium balance. The diagnosis of this condition relies principally on history, careful physical examination and adjunctive data from laboratory studies. All hyponatremic patients are thus by definition overhydrated, but may have varying levels of extracellular fluid volume (intact or disturbed sodium balance).[7]

Intact Sodium Balance

Overhydration, in this situation, does not lead to changes in extracellular fluid volume and only hyponatremia ensues. Serum sodium concentration is tightly regulated principally by the actions of arginine vasopressin (AVP) on the collecting duct. AVP is manufactured in the supraoptic and paraventricular nuclei of the hypothalamus, stored in the

Reprint Requests: Adedayo Onitilo, MD, MSCR, FACP, Marshfield Clinic, Weston Center, 3501 Cranberry Boulevard, Weston, WI 54476, Tel: 715-393-1400, Fax: 715-393-1399, Email: onitilo.adedayo@marshfieldclinic.org

Received: March 13, 2007
1st Revision Received: April 27, 2007
2nd Revision Received: June 8, 2007
Accepted: June 8, 2007
doi:10.3121/cmr.2007.762

posterior pituitary and then released from the pituitary in response to increased serum osmolarity sensed by osmoreceptors in the paraventricular nucleus. AVP release can also be triggered by a decrease in circulating volume (arterial pressure) mediated via baroreceptors. The latter mechanism plays a lesser role in AVP release, as a relatively higher degree of hypovolemia is required to simulate AVP release. AVP induces aquaphores in the cells of the distal collecting duct, allowing movement of water into the hypertonic medullary interstitium. In this way, hyperosmolality is prevented by dilution of sodium ions. A malfunction in any of these mechanisms may result in hyponatremia and, if severe enough, associated symptoms.

Disturbed Sodium Balance

In some diseases, both sodium and water homeostasis go awry, leading the kidney to reabsorb water even though the patient also appears fluid-overloaded or depleted. In both situations, as a result of water retention, the plasma osmolality decreases and hyponatremia ensues. In hypervolemic patients, such as with heart failure or hepatic cirrhosis, retention of sodium and water may continue even though they may have a clinically apparent excess of extracellular fluid volume (i.e., edema or ascites). This occurs because, in an attempt to restore the perfusion pressure to the tissues of the body, these baroreceptors signal the posterior pituitary to release antidiuretic hormone (ADH) resulting in free water reabsorption and hyponatremia, even if the plasma is already dilute. The volume of extracellular fluid needed to maintain such perfusion pressure and avoid stimulation of ADH release has been called the effective circulating blood volume. It may be noted here that although there also is usually a positive sodium balance, its incremental effect is less than the depressive effect of the positive water balance on the serum sodium concentration.[8]

The same thing happens when sodium loss directly leads to hypovolemia and decreases in the true circulating blood volume. This lowers the osmotic threshold at which ADH is secreted.[9] Thus, ADH secretion will persist even if plasma osmolality is <275 mOsm/kg H_2O. This is sometimes seen in patients with gastrointestinal solute loss (e.g., from diarrhea or emesis), third-spacing (e.g., from ileus or pancreatitis), diuretic use and salt-wasting renal disorders. Again, water

Table 1. Major causes of tumor-related hyponatremia.

Group	Mechanism	Causes	Clinical presentation
I. Normal sodium balance			
Ia	Excess ADH	Excess ADH Paraneoplastic syndrome Antineoplastic agents Cyclophosphamide Vinca alkaloids Glucocorticoid deficiency Thyroid hormone deficiency	As SIADH with normal extracellular fluid volume
Ib	Excess intake of free water or pseudohyponatremia	Tumor products Immunoglobulin Paraproteins Excess of hypotonic solutions	Pseudohyponatremia or true water excess not due to SIADH
II. Impaired sodium balance			
IIa	Renal solute conservation	Decreased true circulating blood volume Gastrointestinal causes Reduced salt and water intake GI losses (vomiting and diarrhea) Third spacing Decreased effective circulating blood volume Heart failure Liver cirrhosis	Hypervolemic or hypovolemic with increased or decreased extracellular fluid volume, respectively but hyponatremia not due to disturbed renal handling of Na.
IIb	Renal solute loss	Adrenocortical insufficiency Excess ANP or BNP Ectopic ANP Cerebral salt wasting Renal salt wasting Anticancer drugs Cisplatin Carboplatin	Volume depleted with decreased extracellular fluid volume due to disturbed renal handling of Na.

ADH, antidiuretic hormone; ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

balance is also typically negative in these patients and is actually contributing to the partial correction of the hyponatremia. Therefore, hypovolemic hyponatremia should be viewed from a pathophysiologic standpoint as a disorder of negative sodium balance with inadequate negative water balance to normalize the plasma Na+.[8]

HYPONATREMIA AND TUMOR-RELATED CONDITIONS

About 14% of hyponatremia in medical inpatients is due to underlying tumor-related conditions,[10] but hyponatremia occurs with a similar frequency in patients with tumorous conditions, as with general medical patients, although the distribution of causes is different.[3] The systemic manifestation of many types of tumors and the toxicities of anti-tumor therapy are involved in the pathogenesis of hyponatremia of malignancies.[3,4] They include pathways with intact or disturbed sodium balance and can be broadly classified into four major groups (table 1). In patients with tumors, groups Ia (syndrome of inappropriate secretion of antidiuretic hormone, SIADH) and IIa (depletional states) represent the major categories with approximately equal frequency, making up approximately two-thirds of cases.[3] The tumors most commonly resulting in hyponatremia of the SIADH type are lung, breast and head and neck tumors.[3]

Intact Sodium Balance

GROUP IA

Pituitary Dysfunction

- *Pituitary tumor with normal anterior pituitary function.* Local pituitary tumor may cause exaggerated secretion of AVP, resulting in SIADH despite normal anterior pituitary function,[11,12] although few cases have been reported. In these cases, thyroid and adrenal function testing do not show any abnormalities. However, associated thoracic pathology must be excluded as this is more common.[13]
- *Anterior pituitary hormone deficiency.* While hyponatremia is known to occur in patients with hypopituitarism, severe hyponatremia occurring as the presenting feature of hypopituitarism is quite rare.[14] The hyponatremia usually mimics the laboratory diagnostic criteria of SIADH. However, the hormone studies will usually display hypopituitarism. Hyponatremia is usually completely corrected after administering supplements of corticosteroids and thyroxine. Such hypopituitarism may be associated with a primary pituitary tumor or other tumor-related states, such as Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia.[15] Metastases may also induce a state of hypopituitarism and thus SIADH. Reported cases include intracellular remote metastasis from an adenoid cystic carcinoma of parotid gland origin[16] and metastatic renal cell carcinoma presenting with a bitemporal visual field defect, hyponatremia and panhypopituitarism.[17] Finally, this condition can also be brought about by hypoadrenalocortism as a result of inappropriately tapered corticosteroids.
- *Craniopharyngioma.* Post-surgery, craniopharyngiomas induce a classical triphasic pattern of endogenous vasopressin secretion: (1) an initial phase of symptomatic diabetes insipidus occurring 24 hours after surgery, (2) a phase of inappropriate vasopressin secretion potentially causing hyponatremia and (3) a phase with a return to diabetes insipidus occurring up to 2 weeks later. Such events may also be complicated by cerebral salt wasting (which is discussed under group IIA) and thirst disorders.[18] The hyponatremia that ensues in the second phase may cause a lethal rise in intracranial pressure.[19] It may be noted that a triphasic response can be observed following surgical resection or hypophysectomy due to any intrasellar or suprasellar pathology and this is not exclusive to craniopharyngiomas, although the latter do present with a higher frequency of diabetes insipidus.
- *Post transsphenoidal surgery.* Transient diabetes insipidus is a well-known complication after transsphenoidal surgery. On the other hand, transient hyponatremia has been reported as being a delayed complication of transsphenoidal surgery,[20] and also has been attributed to SIADH, but the details of this type of hyponatremia have not been clarified. About a third of patients develop hyponatremia after transsphenoidal surgery of pituitary adenomas. This usually appears on the 4th to 7th day postoperatively[21] and presents with nausea, vomiting, headache, dizziness, confusion and weakness.[22] Hyponatremia is usually more common in the elderly and patients with macroadenomas and huge pituitary adenomas (although not related to the degree of resection) and usually resolves within 2 weeks.[22] It may be noted that postoperative overadministration of desmopressin acetate (DDAVP) to treat the first phase of diabetes insipidus which occurs on postoperative days 1-3 is also common.

Paraneoplastic Production of ADH

In a minority of patients with tumors, signs and symptoms develop that cannot be explained on the basis of either the mass effect produced by the primary tumor (or its metastases) or the production of a hormone normally associated with the tissue type that has given rise to the malignant tumor. These peculiar symptom complexes are known as paraneoplastic syndromes and may lead to hyponatremia via the ectopic production of ADH. The first clinical case of a patient with ectopic SIADH was presented by Schwartz et al[23] in 1957, when he described two patients with lung cancer who developed hyponatremia associated with continued urinary sodium loss. They postulated that the tumors led to the inappropriate release of ADH, later discovered to consist of AVP. This suggestion was later confirmed since immunoactive AVP has been noted to be elevated in plasma of patients with bronchogenic carcinoma,[24] as well as in patients with a cancer of the digestive tract.[25] Some tumors may actually demonstrate multiple hormone production and clinical and laboratory evidence of both the ectopic adrenocorticotropic hormone and ADH syndromes.[26] However, almost all the tumors that produced AVP were small cell lung cancers (SCLC) and much less commonly, non-

SCLCs.[27,28] Collected series show that about l0% to 15% of such patients have clinically evident humoral hyponatremia at time of presentation[28,29] while up to 70% of patients with SCLC have significant elevations of plasma AVP detectable by radioimmunoassay that tend to normalize with successful therapy.[30]

Other series of patients have revealed that SIADH also occurs in 3% of patients with head and neck cancer.[31,32] Head and neck lesions associated with the development of SIADH often tend to be located in the oral cavity, and less often in the larynx, nasopharynx, hypopharynx, nasal cavity, maxillary sinus, parapharyngeal space, salivary glands and oropharynx.[32] Despite a major association of ectopic ADH secretion with SCLC and head and neck tumors, a broad spectrum of malignant tumors have also been reported to cause SIADH; however, most of these observations have been in case reports of very few patients and include such tumors as olfactory neuroblastomas, small cell neuroendocrine carcinomas, adenoid cystic carcinomas, undifferentiated carcinomas and sarcomas that result in ectopic ADH production.

Medical Anti-Cancer Therapy

Antineoplastic agents such as vincristine, vinblastine and cyclophosphamide are well known to induce hyponatremia.[4] The mechanism seems to be cytotoxicity affecting paraventricular and supraoptic neurons.[31] There have been several reports associating vincristine with SIADH, and some of these reports documented inappropriately high serum levels of vasopressin as well as the recurrence of SIADH during subsequent therapy with vincristine.[33] Vinblastine has also been reported to cause severe hyponatremia and SIADH.[34] Similarly, cyclophosphamide therapy has been associated with hyponatremia and SIADH, with reversible SIADH reported in two patients treated with high dose cyclophosphamide (50 mg/kg).[33]

GROUP IB

Drug-Induced Polydipsia

This condition results from excessive drinking of water that can accompany ingestion of phenothiazines used as antiemetic agents.

Pseudohyponatremia

Pseudohyponatremia is present when spuriously low sodium levels are recorded due to elevated levels of other solutes such as glucose. Normal or high plasma osmolarity with hyponatremia is the clinical definition of pseudohyponatremia. Classically, pseudohyponatremia is divided into conditions in which the measured and calculated serum osmolalities are the same, hyperglycemia or uremia, and those in which there is an osmolar gap. Some osmoles are clearly present and usually measured, but are not recognized. The source of unmeasured osmoles may be endogenous (lipids or proteins) or exogenous alcohols (e.g., ethanol, ethylene glycol, methanol, or isopropyl alcohol). Hyperglycemia can accompany use of steroids in the treatment of nausea, compression syndromes and lymphoma.

Dilutional Hyponatremia

Initially dilutional hyponatremia has been reported with hydration protocols, especially in pediatric cancer units.[35] Overhydration with hypotonic solutions will especially result in hyponatremia, if one of the other mechanisms is contributing as well, such as decreased circulating volume or excess ADH.[35] Other mechanisms are the use of hypotonic solutions during irrigation of closed body spaces which may lead to substantial perioperative fluid and electrolyte shifts. The most commonly reported are a syndrome occurring during transurethral resection of prostate,[36,37] and a similar syndrome described in women undergoing transcervical endometrial ablation[38] which are both characterized by a spectrum of symptoms that may range from asymptomatic hyponatremia to convulsions, coma and death. Such potentially serious consequences require prompt recognition and appropriate management of this water intoxication syndrome.

Disturbed Sodium Balance

GROUP IIA

Decreased True Circulating Blood Volume

- *Intrinsic renal disease by antineoplastic therapy.* This condition is usually iatrogenic and can follow administration of drugs, such as cisplatin,[39] which interferes with the absorption of sodium by directly damaging renal tubules.
- *GI losses.* Emesis or diarrhea secondary to antineoplastic therapy can lead to hyponatremia.
- *Cerebral salt wasting.* Cerebral salt wasting can be seen in critically ill patients following surgery for intracranial tumors or accompanying diagnosis of intracranial tumors.[40] The exact pathophysiology is unknown. It may be related to interruptions in neurohypophysial pathways, either iatrogenic or secondary to the anatomical position of the tumor. These may result in increased secretion of brain and/or atrial natriuretic peptides, resulting in inappropriate increased renal excretion of sodium. Cerebral salt wasting is often confused with SIADH because both syndromes share certain key features: low serum sodium, low serum osmolality, a higher urine osmolality than serum osmolality and an elevated urinary sodium concentration.[41] Furthermore, what distinguishes cerebral salt wasting from SIADH (extracellular fluid contraction and inappropriately negative sodium balance) is often difficult to establish beyond a reasonable doubt, even with invasive testing or blood markers.[42,43] Nevertheless, it is important to make this distinction because the management of the two conditions differs markedly, and if the wrong treatment is chosen, there can be serious consequences, including worsening of hyponatremia and, more rarely, cerebral ischemia.[42]

Decreased Effective Circulating Blood Volume

This hyponatremic mechanism is uncommon in the tumor patient and can accompany conditions such as congestive heart failure that complicates use of antineoplastic therapy

agents (e.g., anthracyclines). Another condition that may be associated is minimal change nephrotic syndrome associated with solid tumors.[44] Patients present with features of peripheral edema but paradoxically have a decrease in effective circulating volume with increased thirst, increased AVP production and decreased glomerular filtration rate, resulting in delivery of concentrated urine to the collecting duct.

GROUP IIB

Adrenal Metastases

If a patient with an advanced tumor presents with unexplained and protracted nausea, vomiting and weakness, particularly if accompanied by hyponatremia and normal potassium levels, adrenal insufficiency due to adrenal metastases should be considered.[45] This can occur with patients suffering from advanced breast cancer[45] or colon carcinoma.[46] Primary adrenal lymphoma involving both adrenals has also been reported to result in hyponatremia and hyperkalemia secondary to adrenal insufficiency.[47]

Paraneoplastic Production of Atrial Natriuretic Peptide

One-third of patients with SCLC and hyponatremia have no evidence of ectopic AVP production. Studies, therefore, have sought to distinguish patients with hyponatremia caused by elevated AVP versus those with ectopic atrial natriuretic peptide. Gross et al[48] found that 17 of 21 SCLC cell lines expressed atrial natriuretic peptide. Eleven of these 21 patients were hyponatremic at presentation and their cell lines expressed either atrial natriuretic peptide (4 cell lines), AVP (2 cell lines) or both (5 cell lines). The production of AVP was closely linked to the presence of hyponatremia in patients with SCLC whereas atrial natriuretic peptide production did not have as strong an association with the presence of hyponatremia. More recently,[49] however, it has been shown that some patients with SCLC and hyponatremia can have elevated atrial natriuretic peptide levels at presentation without elevation of AVP. All patients who presented with hyponatremia and elevated atrial natriuretic peptide showed a decline in serum sodium following fluid restriction, whereas patients with SCLC and elevated AVP had normalized serum sodium levels. The combination of hyponatremia and elevated atrial natriuretic peptide was associated with a persistent natriuresis and inappropriately low aldosterone levels despite sodium restriction, suggesting atrial natriuretic peptide suppression of the aldosterone axis. Management of patients with hyponatremia and SCLC should be guided by the knowledge that some patients with SCLC have ectopic production of atrial natriuretic peptide as the cause of their hyponatremia and may need to be managed differently than SIADH.[49]

CLINICAL FEATURES

The symptoms that may be seen with hyponatremia are primarily neurologic and are related both to the severity and particularly to the rapidity of onset of change in the plasma sodium concentration. The presence of cerebral overhydration generally correlates closely with severity of symptoms. Nausea and malaise are the earliest findings and may be seen when the plasma sodium concentration falls below 125 mEq/L to 130 mEq/L. This may be followed by headache, lethargy and obtundation and eventually seizures, coma and respiratory arrest, if the plasma sodium concentration falls below 115 mEq/L to 120 mEq/L.[50] Noncardiogenic pulmonary edema has also been described.[51] Hyponatremic encephalopathy may be reversible, although permanent neurologic damage or death may occur.[52] Overly rapid correction also may be deleterious, especially in patients with chronic asymptomatic hyponatremia. These symptoms of hyponatremia may predate or accompany diagnosis or intervention for the tumor and are present only in a minority of patients.[29] The symptoms are rarely present at sodium levels higher than 125 mEq/L. Diagnosis of hyponatremia with a tumor may not correlate with stage, anatomical spread or response to therapy.

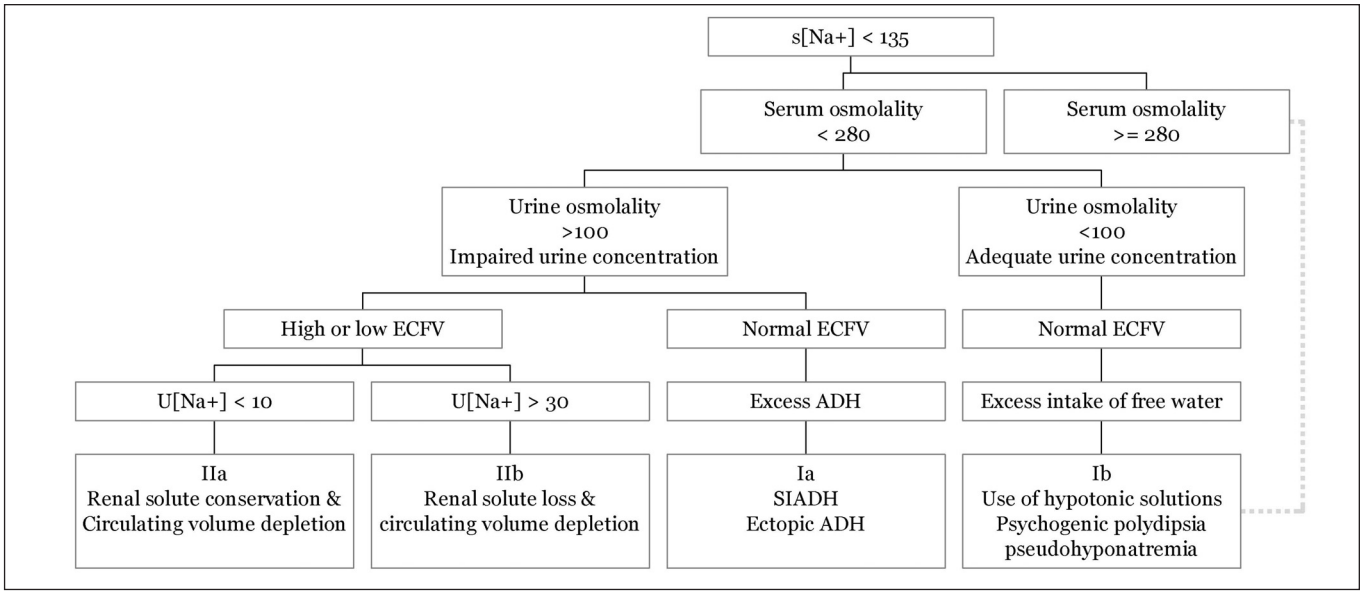

Figure 1. Diagnostic pathway in hyponatremia.

DIAGNOSIS

Hyponatremia associated with tumors is a diagnosis of exclusion. Spurious causes such as hyperglycemia (1.6 mmol/L decrease in Na^+ for each 5 mmol/L increase in glucose) should be excluded. In addition to a diagnosis of the tumor, an astute note of medications and other therapeutic interventions should be obtained in the clinical history. Important laboratory studies include serum and urinary Na^+, osmolarity and creatinine, urinary potassium and serum uric acid. SIADH is associated with normovolemia, low serum uric acid and inappropriately increased urine fractional excretion of sodium. Measurement of cortisol and thyroid hormones will exclude adrenal insufficiency and hypothyroidism as potential causes. Patients with hypervolemia (edema) should be evaluated for congestive heart failure, nephrosis and liver disease. This diagnostic approach is depicted in figure 1.

Urine Osmolality

Normally, when the body is faced with a water load, serum osmolality is decreased, ADH is suppressed and excess free water is excreted in very dilute urine (osmolality as low as 50-100 mOsm/kg). The normal response to hyponatremia (which is maintained in primary polydipsia) is to completely suppress ADH secretion, resulting in the excretion of a maximally dilute urine with an osmolality below 100 mOsmol/kg and a specific gravity ≤1.003. Values above this level indicate an inability to normally excrete free water that is generally due to continued secretion of ADH. Most hyponatremic patients have a relatively marked impairment in urinary dilution that is sufficient to maintain the urine osmolality at 300 mOsm/kg or greater. Three hyponatremic disorders may present with a urine osmolality below 100 mOsm/kg: (1) malnutrition, often in beer drinkers, in which dietary solute intake (sodium, potassium, protein) and therefore solute excretion is so low that the rate of water excretion is markedly diminished even though urinary dilution is intact; (2) reset osmostat after a water load appropriately suppresses ADH release with the major clinical clue to the presence of this disorder being a moderately reduced plasma sodium concentration (usually between 125 and 135 mEq/L) that is stable on multiple measurements; (3) primary polydipsia.

Urine Sodium Concentration

In general, a spot test showing urine sodium concentration of <30 mmol/L differentiates patients with hypovolemic hyponatremia (unless there is renal salt-wasting due most often to diuretic therapy or cerebral salt wasting) from patients with euvolemic hyponatremia (who have urine sodium concentration >30 mmol/L on spot testing) and whose rate of sodium excretion is determined by sodium intake.[53]

Plasma Uric Acid and Urea Concentrations

The initial water retention and volume expansion in SIADH leads to another frequent finding opposite that typically seen with volume depletion: hypouricemia (plasma uric acid concentration <238 μmol/L) due to increased uric acid excretion in the urine.[54,55] Water retention can also lead to urinary urea wasting and the BUN may fall to below 1.8 mmol/L.[56]

SIADH Criteria

- A fall in the plasma osmolality
- An inappropriately elevated urine osmolality (above 100 mOsm/kg and usually above 300 mOsm/kg)
- A urine sodium concentration usually above 30 mmol/L
- A relatively normal to low plasma urea and creatinine concentration
- Normal adrenal and thyroid function

TREATMENT

The initial adaptation of the brain to hyponatremia includes loss of water, sodium, potassium and chloride into the cerebrospinal fluid; later adaptation consists of the loss of organic osmolytes. Adaptation of the brain to hyponatremia causes potential problems during therapy, as re-adaptation requires a considerably longer time. Rapid correction of hyponatremia may lead to the development of the osmotic demyelination syndrome. Although the ideal treatment for severe hyponatremia remains controversial, a consensus regarding therapeutic guidelines for tumor-related hyponatremia has not yet emerged. The rate of correction and the type of infusate depend on the duration and cause of the hyponatremia, clinical presentation, volume status, renal function and the serum potassium level. Also, treatment of the underlying tumor may be associated with resolution of hyponatremia.

The severity of hyponatremia does not depend on stage or anatomical site of disease. However, recurrence of hyponatremia due to SIADH may signal relapse, for example, in patients with SCLC.[29] Results of a few available studies differ on the prognosis of patients with tumors and hyponatremia. While no effect on prognosis was found in the study by List et al,[29] a deleterious effect on prognosis has been found in other studies on hospitalized patients and patients with tumors and hyponatremia.[3] What is certain is that hyponatremia is not an uncommon condition that should be expected in patients diagnosed and being treated for malignancies. Elucidation of the etiology of hyponatremia on a case-by-case basis and appreciation of the presence and severity of complications are required to institute the proper intervention(s) to reduce morbidity and mortality.

Treatment of hyponatremia is important in preventing and reversing the neurologic sequelae, as well as improving quality of life in patients with tumor-related conditions.[57] The appropriate intervention depends on the pathophysiology, acuity, severity and symptomatology of hyponatremia.

Hyponatremia with Intact Sodium Balance (Ia)

Mild asymptomatic hyponatremia (above 125 mEq/L of sodium) secondary to SIADH may be treated with fluid restriction,

typically 500 cc/day to 1000 cc/day or 60% of total fluid output (sum of insensible and urinary output). Demeclocycline, a tetracycline analog which negates the effects of AVP at the level of renal tubules, may also be used at a dose of 100 mg to 300 mg 3 to 4 times a day. The effect of this drug may be delayed for 1 week to 2 weeks. AVP receptor antagonists may also be used. Only one has US Federal Drug Administration (FDA) approval, conivaptan hydrochloride (see below under hypervolemic hyponatremia) and although this medication is well tolerated as compared to other agents for the treatment of SIADH, the drug is only available intravenously. Thus, if the SIADH is caused by a tumor that will not resolve, this agent cannot be continued in the outpatient setting and is not a reasonable choice. Oral formulations are currently undergoing trials.[58]

Aggressive correction can lead to a potentially fatal condition called pontine myelinolysis associated with headaches, altered mental status, diminished visual acuity and quadriplegia. The exact mechanism by which this occurs is unknown. It is thought to be related to sudden loss of tonicity of neural cells with an increase in extracellular fluid osmolality resulting in necrosis. Therefore, in asymptomatic patients, Na^+ should not be raised by more than 8 mmol/L/24 hours, and in symptomatic patients, by no more than 10 mmol/L/24 hours to 12 mmol/L/24 hours.[59]

If there is inadvertent over-correction of hyponatremia, osmotic demyelination can be avoided by rapid re-induction of the hyponatremia via administration of hypotonic fluids (via oral and intravenous routes) combined with DDAVP. This will induce a prompt decline in the serum sodium concentration with an acceptable final gradient of correction. This maneuver is reported to be well-tolerated without untoward effects[60] and can potentially avoid the adverse outcome reported for inadvertent overcorrection.[61]

USE OF SALINE INFUSIONS IN SEVERE HYPONATREMIA

In severe cases with encephalopathy, 3% hypertonic saline can also be used to increase free water excretion by the kidneys. It has been suggested that the appropriate infusion rate for hypertonic saline in euvolemic hyponatremia be based on a calculated sodium deficit being infused (mmol/hour) and calculated by the total body water multiplied by the desired correction rate (mmol/L/hour).[59,62] Thus if 3% saline were used, this would then require a volume/hour equal to about twice the calculated sodium infusion rate to achieve this as it contains 513 mmol Na/L. This nevertheless is counterintuitive because euvolemic hyponatremia is a state of water excess and the principal determinant of plasma sodium concentration is total body water. Patients do not have a problem with sodium handling and if 1 liter of infusate were given, assuming the patient is sodium replete, all the sodium will be excreted in a volume that is dependent on urine osmolality. We therefore suggest a different equation for the infusion rate that will raise the serum sodium concentration by 0.5 mmol/L/hour as follows (derivation is provided in Appendix 1):

> Infusion rate in cc/h = [TBW – c]*500/[sNa*c]
> where c is given by ((iOsm/uOsm) – 1), where iOsm and uOsm are infusate osmolality and urine osmolality, respectively.

For example, taking a case from the literature:[35]

> A 19-year-old man with relapsed acute lymphoblastic leukaemia (ALL), who had developed panhypopituitarism after an episode of meningitis underwent a preconditioning protocol before bone marrow transplantation. His serum sodium concentration was 138 mmol/L. He received 3 L/m^2 per 24 h of 0.18% NaCl and 4.3% dextrose for 48 h (approximately 80 mL/kg per day, or twice normal maintenance fluids for his size). On the third day, he developed generalized seizures and had a serum sodium concentration of 124 mmol/L. His urinary sodium was 116 mmol/L and urine osmolarity of 511 mOsm/L. His weight had increased by 4.3 kg over 48 h, and he had received his usually prescribed dose of DDAVP.

He would certainly need a 3% saline infusion. Assuming a weight of 50 kg, the rate of infusion of 3% saline is given by (c = (900 / 511) – 1 = 0.8 for 3% saline; TBW = 0.6 x body weight):

$$(((50 * 0.6) – 0.8) * 500) / (120 * 0.8) = 152 \text{ cc/h}$$

Obviously he would have to have volume restriction and his normal dose of DDAVP withheld until the sodium returns to normal. This infusion should be followed by close monitoring of serum sodium every 2 hours to ensure that the predicted rate of correction ensues. Although the main use of 3% saline is in syndromes of excess ADH, as in this patient, it may also be used in acute hyponatremia precipitated by use of hypotonic solutions in patients with true circulating volume depletion,[35] but it must be closely monitored as repletion of the circulating volume may lead to free water diuresis from removal of the non-osmotic stimulus to ADH secretion and a dangerous jump in serum sodium levels.

Hyponatremia with Disturbed Sodium Balance (IIb)

TRUE CIRCULATING VOLUME DEPLETION

In states of true volume depletion, administered sodium and water will initially be retained. In this setting, isotonic saline corrects the hyponatremia and thus asymptomatic hyponatremia due to cerebral salt wasting or extracellular fluid volume depletion should be treated with infusion of saline. Recognition and withdrawal of inciting agents is an important accompaniment. In the case of cisplatin-induced renal salt wasting, it may take several weeks for recovery of renal function.

Management of cerebral salt wasting includes treatment of the underlying cerebral disorder, volume resuscitation and sodium replacement.[64] Generally, volume and sodium repletion is accomplished with intravenous isotonic saline

solutions and oral salt tablets with hypertonic saline reserved for particularly acute or refractory cases. Correction of hyponatremia at the rates suggested for SIADH is most safe and appropriate in cases where hyponatremia has been present for an extended period of time. It may be necessary to enhance renal tubular sodium absorption with mineralocorticoids, such as fludrocortisone acetate, if there are excessive urinary sodium losses. Intravascular volume expansion in the presence of excessive natriuresis of cerebral salt wasting requires a large sodium and water intake, and thus, inhibition of natriuresis with fludrocortisone can effectively reduce the sodium and water intake required for hypervolemia and prevent hyponatremia at the same time.[65,66] In a randomized controlled study, Hasan et al[67] found that oral or intravenous fludrocortisone, 0.2 mg twice daily, reduced the frequency of a negative sodium balance and natriuresis. Problems with the use of fludrocortisone, however, are hypokalemia, fluid overload and hypertension, which must be carefully monitored. It should also be pointed out that some hyponatremic patients may have concurrent SIADH and cerebral salt wasting. Often SIADH first appears and then cerebral salt wasting becomes more significant a few days after the event.

EFFECTIVE CIRCULATING VOLUME DEPLETION

Restricting water intake is the mainstay of therapy in hyponatremic patients with heart failure, although this is often not tolerable because of the intense stimulation of thirst. Water restriction (without sodium restriction) is not expected to lead to increased hypovolemia and worsening of renal function. In refractory cases, the combination of an angiotensin-converting enzyme inhibitor and a loop diuretic also may induce an elevation in the plasma sodium concentration. Angiotensin-converting enzyme inhibitors (via the local generation of prostaglandins) appear to antagonize the effect of ADH on the collecting tubules, thereby decreasing water reabsorption at this site. Loop diuretic increases water delivery to the collecting tubules which, due to the decrease in ADH secretion and responsiveness are now less permeable to water.

An alternative may be the use of AVP receptor antagonists that are selective for the V2 (antidiuretic) receptor, which are undergoing testing in humans. These agents produce a selective water diuresis (without affecting sodium and potassium excretion). Conivaptan hydrochloride injection (Vaprisol) has been approved for the intravenous treatment of hypervolemic hyponatremia in hospitalized patients.[68] Conivaptan is also a potent inhibitor of CYP3A4 and, as an oral formulation, increases the area under the curve of midazolam 2-fold to 3-fold, simvastatin 3-fold and amlodipine 2-fold. This level of interaction is what prevented the oral formulation from being pursued for FDA approval. Conivaptan should not be mixed with lactated Ringer's or 0.9% sodium chloride since it has only been tested in 5% dextrose solution. The recommended dose of conivaptan is a loading dose of 20 mg intravenously administered over 30 minutes followed by 20 mg infused over 24 hours. Following the initial day of therapy, conivaptan should be administered for an additional 1 day to 3 days as a continuous infusion of 20 mg/day.

CONCLUSION

Hyponatremia occurs quite frequently in patients with tumors. The systemic manifestation of many types of tumors and the toxicities of cancer therapy are involved in the pathogenesis of hyponatremia of malignancies. Early detection and management is crucial to improve the patient's prognosis. There is, however, a need for further study into the pathophysiology and the effect of hyponatremia on the outcome of patients with tumors.

ACKNOWLEDGMENTS

The authors thank Marshfield Clinic Research Foundation for its support through the assistance of Linda Weis and Alice Stargardt in the preparation of this manuscript.

REFERENCES

1. Wakui A. Electrolyte abnormalities associated with cancer: a review. Gan To Kagaku Ryoho 1986;13:2031-2038.
2. U.S. Food and Drug Administration. Center for Biologics Evaluation and Research. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. http://www.fda.gov/cber/gdlns/toxvac.htm. Accessed April 25, 2007.
3. Berghmans T, Paesmans M, Body JJ. A prospective study on hyponatraemia in medical cancer patients: epidemiology, aetiology and differential diagnosis. Support Care Cancer 2000;8:192-197.
4. Berghmans T. Hyponatremia related to medical anticancer treatment. Support Care Cancer 1996;4:341-350.
5. Bennettt HE, Bishop M, Zadik TD, Lincoln NB. Cognitive impairment after transurethral resection of the prostate (TURP). Disabil Rehabil 2004;26:1381-1387.
6. Freda BJ, Davidson MB, Hall PM. Evaluation of hyponatremia: a little physiology goes a long way. Cleve Clin J Med 2004;71:639-650.
7. Mange K, Matsuura D, Cizman B, Soto H, Ziyadeh FN, Goldfarb S, Neilson EG. Language guiding therapy: the case of dehydration versus volume depletion. Ann Intern Med 1997;127:848-853.
8. Kurtz I, Nguyen MK. Evolving concepts in the quantitative analysis of the determinants of the plasma water sodium concentration and the pathophysiology and treatment of the dysnatremias. Kidney Int 2005;68:1982-1993.
9. Robertson GL, Athar S. The interaction of blood osmolality and blood volume in regulating plasma vasopressin in man. J Clin Endocrinol Metab 1976;42:613-620.
10. Gill G, Huda B, Boyd A, Skagen K, Wile D, Watson I, van Heyningen C. Characteristics and mortality of severe hyponatraemia—a hospital-based study. Clin Endocrinol (Oxf) 2006;65:246-249.
11. Kanda M, Omori Y, Shinoda S, Yamauchi T, Tamemoto H, Kawakami M, Ishikawa SE. SIADH closely associated with non-functioning pituitary adenoma. Endocr J 2004;51:435-438.
12. Hung SC, Wen YK, Ng YY, Yang WC. Inappropriate antidiuresis associated with pituitary adenoma—mechanisms not involving inappropriate secretion of vasopressin. Clin Nephrol 2000;54:157-160.

13. Zogheri A, Di Mambro A, Mannelli M, Serio M, Forti G, Peri A. Hyponatremia and pituitary adenoma: think twice about the etiopathogenesis. J Endocrinol Invest 2006;29:750-753.
14. Lin SH, Hung YH, Lin YF. Severe hyponatremia as the presenting feature of clinically non-functional pituitary adenoma with hypopituitarism. Clin Nephrol 2002;57:85-88.
15. Yamaguchi H, Nakamura H, Mamiya Y, Yamamoto Y, Tajika K, Sugihara H, Gomi S, Inokuchi K, Hasegawa S, Shibazaki T, Dan K, Wakabayashi I. Acute lymphoblastic leukemia with isolated adrenocorticotropic hormone deficiency. Intern Med 1997;36:819-821.
16. Kawamata T, Harashima S, Kubo O, Hori T. Intrasellar remote metastasis from adenoid cystic carcinoma of parotid gland: case report. Endocr J 2006;53:659-663.
17. Liu H, Yamaki T, Oka S, Koyanagi I, Houkin K. Metastatic renal cell carcinoma mimicking pituitary adenoma: case report. Neurol Med Chir (Tokyo) 2005;45:418-422.
18. Ghirardello S, Hopper N, Albanese A, Maghnie M. Diabetes insipidus in craniopharyngioma: postoperative management of water and electrolyte disorders. J Pediatr Endocrinol Metab 2006;19:413-421.
19. Bohn D, Davids MR, Friedman O, Halperin ML. Acute and fatal hyponatraemia after resection of a craniopharyngioma: a preventable tragedy. QJM 2005;98:691-703.
20. Sata A, Hizuka N, Kawamata T, Hori T, Takano K. Hyponatremia after transsphenoidal surgery for hypothalamo-pituitary tumors. Neuroendocrinology 2006;83:117-122.
21. Adams JR, Blevins LS Jr, Allen GS, Verity DK, Devin JK. Disorders of water metabolism following transsphenoidal pituitary surgery: A single institution's experience. Pituitary 2006;9:93-99.
22. Wei T, Zuyuan R, Changbao S, Renzhi W, Yi Y, Wenbin M. Hyponatremia after transspheniodal surgery of pituitary adenoma. Chin Med Sci J 2003;18:120-123.
23. Schwartz WB, Bennett W, Curelop S, Bartter FC. A syndrome of renal sodium loss and hyponatremia probably resulting from inappropriate secretion of antidiuretic hormone. Am J Med 1957;23:529-542.
24. Morton JJ, Kelly P, Padfield PL. Antidiuretic hormone in bronchogenic carcinoma. Clin Endocrinol (Oxf) 1978; 9:357-370.
25. Bernard-Weil E, Jost JL, Vayre P. New data on the adrenal-post-pituitary system of cancer patients. Ann Endocrinol (Paris) 1986;47:201-203.
26. Suzuki H, Tsutsumi Y, Yamaguchi K, Abe K, Yokoyama T. Small cell lung carcinoma with ectopic adrenocorticotropic hormone and antidiuretic hormone syndromes: a case report. Jpn J Clin Oncol 1984;14:129-137.
27. Padfield PL, Morton JJ, Brown JJ, Lever AF, Robertson JI, Wood M, Fox R. Plasma arginine vasopressin in the syndrome of antidiuretic hormone excess associated with bronchogenic carcinoma. Am J Med 1976;61:825-831.
28. Shapiro J, Richardson GE. Hyponatremia of malignancy. Crit Rev Oncol Hematol 1995;18:129-135.
29. List AF, Hainsworth JD, Davis BW, Hande KR, Greco FA, Johnson DH. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in small-cell lung cancer. J Clin Oncol 1986;4:1191-1198.
30. Odell WD, Wolfsen AR. Humoral syndromes associated with cancer. Annu Rev Med 1978;29:379-406.
31. Sorensen JB, Andersen MK, Hansen HH. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) in malignant disease. J Intern Med 1995;238:97-110.
32. Ferlito A, Rinaldo A, Devaney KO. Syndrome of inappropriate antidiuretic hormone secretion associated with head neck cancers: review of the literature. Ann Otol Rhinol Laryngol 1997;106:878-883.
33. Yeung SC, Chiu AC, Vassilopoulou-Sellin R, Gagel RF. The endocrine effects of nonhormonal antineoplastic therapy. Endocr Rev 1998;19:144-172.
34. Zavagli G, Ricci G, Tataranni G, Mapelli G, Abbasciano V. Life-threatening hyponatremia caused by vinblastine. Med Oncol Tumor Pharmacother 1988;5:67-69.
35. Duke T, Kinney S, Waters K. Hyponatraemia and seizures in oncology patients associated with hypotonic intravenous fluids. J Paediatr Child Health 2005;41:685-686.
36. Iihoshi M, Sakuragi T, Higa K, Hamada T. Severe hyponatremia during transurethral resection of prostate. Masui 2005;54:414-417.
37. Issa MM, Young MR, Bullock AR, Bouet R, Petros JA. Dilutional hyponatremia of TURP syndrome: a historical event in the 21st century. Urology 2004;64:298-301.
38. Hwang CB, Hui YL, Liu WC, Chu KK, Wang YL, Ho AC. Absorption of irrigating fluid during transcervical resection of endometrium—a report of two cases. Acta Anaesthesiol Sin 1997;35:45-50.
39. Iyer AV, Krasnow SH, Dufour DR, Arcenas AS. Sodium-wasting nephropathy caused by cisplatin in a patient with small-cell lung cancer. Clin Lung Cancer 2003;5:187-189.
40. Sane T, Rantakari K, Poranen A, Tahtela R, Valimaki M, Pelkonen R. Hyponatremia after transsphenoidal surgery for pituitary tumors. J Clin Endocrinol Metab 1994; 79:1395-1398.
41. Maesaka JK, Gupta S, Fishbane S. Cerebral salt-wasting syndrome: does it exist? Nephron 1999;82:100-109.
42. Gutierrez OM, Lin HY. Refractory hyponatremia. Kidney Int 2007;71:79-82.
43. Oh MS, Carroll HJ. Cerebral salt-wasting syndrome. We need better proof of its existence. Nephron 1999;82:110-114.
44. Meyrier A, Delahousse M, Callard P, Rainfray M. Minimal change nephrotic syndrome revealing solid tumors. Nephron 1992;61:220-223.
45. Bausewein C, Kuhnbach R, Haberland B. Adrenal insufficiency caused by bilateral adrenal metastases — a rare treatable cause for recurrent nausea and vomiting in metastatic breast cancer. Onkologie 2006;29:203-205.
46. Omoigui NA, Cave WT Jr, Chang AY. Adrenal insufficiency. A rare initial sign of metastatic colon carcinoma. J Clin Gastroenterol 1987;9:470-474.
47. Toubai T, Akama H, Takagawa M, Ishida S, Kasai M, Tanaka J, Imamura M. Primary adrenal lymphoma: a case report and literature review in Japan. Rinsho Ketsueki 2002;43:851-856.
48. Gross AJ, Steinberg SM, Reilly JG, Bliss DP Jr, Brennan J, Le PT, Simmons A, Phelps R, Mulshine JL, Ihde DC, Johnson BE. Atrial natriuretic factor and arginine vasopressin production in tumor cell lines from patients with lung cancer and their relationship to serum sodium. Cancer Res 1993;53:67-74.
49. Chute JP, Taylor E, Williams J, Kaye F, Venzon D, Johnson BE. A metabolic study of patients with lung cancer and hyponatremia of malignancy. Clin Cancer Res 2006; 12:888-896.
50. Ellis SJ. Severe hyponatraemia: complications and treatment. QJM 1995;88:905-909.
51. Ayus JC, Varon J, Arieff AI. Hyponatremia, cerebral edema, and noncardiogenic pulmonary edema in marathon runners. Ann Intern Med 2000;132:711-714.
52. Moritz ML, Ayus JC. The pathophysiology and treatment of hyponatraemic encephalopathy: an update. Nephrol Dial Transplant 2003;18:2486-2491.
53. Graber M, Corish D. The electrolytes in hyponatremia. Am J Kidney Dis 1991;18:527-545.
54. Beck LH. Hypouricemia in the syndrome of inappropriate secretion of antidiuretic hormone. N Engl J Med 1979;301:528-530.

55. Decaux G, Namias B, Gulbis B, Soupart A. Evidence in hyponatremia related to inappropriate secretion of ADH that V1 receptor stimulation contributes to the increase in renal uric acid clearance. J Am Soc Nephrol 1996;7:805-810.
56. Decaux G, Schlesser M, Coffernils M, Prospert F, Namias B, Brimioulle S, Soupart A. Uric acid, anion gap and urea concentration in the diagnostic approach to hyponatremia. Clin Nephrol 1994;42:102-108.
57. Adrogue HJ. Consequences of inadequate management of hyponatremia. Am J Nephrol 2005;25:240-249.
58. Schrier RW, Gross P, Gheorghiade M, Berl T, Verbalis JG, Czerwiec FS, Orlandi C; SALT investigators. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-2112.
59. Adrogue HJ, Madias NE. Hyponatremia. N Engl J Med 2000;342:1581-1589.
60. Soupart A, Ngassa M, Decaux G. Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. Clin Nephrol 1999;51:383-386.
61. Lasheen I, Doi SA, Al-Shoumer KA. Glucocorticoid replacement in panhypopituitarism complicated by myelinolysis. Med Princ Pract 2005;14:115-117.
62. Smith DM, McKenna K, Thompson CJ. Hyponatraemia. Clin Endocrinol (Oxf) 2000;52:667-678.
63. Doi SA. Treatment of euvolemic hyponatremia: sodium repletion or water depletion? Clin Endocrinol (Oxf) 2003;59:142.
64. Harrigan MR. Cerebral salt wasting syndrome. Crit Care Clin 2001;17:125-138.
65. Mori T, Katayama Y, Kawamata T, Hirayama T. Improved efficiency of hypervolemic therapy with inhibition of natriuresis by fludrocortisone in patients with aneurysmal subarachnoid hemorrhage. J Neurosurg 1999;91:947-952.
66. Betjes MG. Hyponatremia in acute brain disease: the cerebral salt wasting syndrome. Eur J Intern Med 2002;13:9-14.
67. Hasan D, Lindsay KW, Wijdicks EF, Murray GD, Brouwers PJ, Bakker WH, van Gijn J, Vermeulen M. Effect of fludrocortisone acetate in patients with subarachnoid hemorrhage. Stroke 1989;20:1156-1161.
68. Verbalis JG. AVP receptor antagonists as aquaretics: review and assessment of clinical data. Cleve Clin J Med 2006;73 (Suppl 3):S24-S33.

Author Affiliation

Adedayo A. Onitilo, MD, MSCR, FACP
Department of Hematology/Oncology
Marshfield Clinic Weston Center
3501 Cranberry Boulevard
Weston, Wisconsin

Ebenezer Kio, MD
Southern Ohio Medical Center Cancer Center
1121 Kinneys Lane
Portsmouth, Ohio

Suhail A. R. Doi, MBBS, FRCP, PhD
Department of Medicine
Mubarak Al Kabeer Teaching Hospital
Jabriya, Kuwait and
Department of Medicine, Kuwait University
Kuwait

APPENDIX I

A rise in serum sodium concentration (ΔNa in mmol/L) after infusion of 1 liter of infusate can be given by the following equation:[59]

[(new total body Na)/(new total body water)] – initial serum sodium concentration

After 1 liter of infusate this is calculated by:

$$[(sNa \times TBW) + iNa]/(TBW + 1) \qquad \text{Eq 1}$$

using initial serum sodium (sNa in mmol/L), total body water (TBW in L, approximately 0.5 to 0.6 times body weight in kg) and infusate sodium concentration (iNa in mmol/L). This was reduced by Adrogue and Madias[59] to:

$$(iNa - sNa)/(TBW + 1) \qquad \text{Eq 2}$$

This nevertheless is counterintuitive because euvolemic hyponatremia is a state of water excess and the principal determinant of plasma sodium concentration is total body water. Patients do not have a problem with sodium handling and if 1 liter of infusate were given, assuming the patient is sodium replete, all the sodium will be excreted in a volume that is dependent on urine osmolality. The corrected Eq 1 should then read:[63]

$$[(sNa \times TBW)/(TBW - c)] - sNa \qquad \text{Eq 3}$$

where c is the net volume lost (the volume in which the sodium is excreted by the kidneys corrected for the 1 liter infused) and is given by:

$$c = [1 \times (iOsm/uOsm)] - 1 = [iOsm/uOsm] - 1 \qquad \text{Eq 4}$$

where 1 represents the volume of the infusate, and iOsm and uOsm are infusate and urine osmolality, respectively. It should be noted here that in the initial derivation by Doi[63] the subtraction of 1 liter (infusate) was inadvertently omitted. This then reduces to two practical and corrected equations for clinical use:

$$[sNa.c]/[TBW - c] = \Delta Na \qquad \text{Eq 5}$$

and

$$[TBW - c]/[sNa.c)] = \Delta infusate \qquad \text{Eq 6}$$

where ΔNa and Δinfusate are the sodium concentration change after 1 liter of infusate (in mmol/L) and the volume of infusate (in L) that would increase serum sodium by 1 mmol/L, respectively. Since the rate of correction should not exceed 0.5 mmol/L/hour, the rate of infusate in cc/hour reduces to:

$$cc/h = [TBW - c]*500/[sNa*c] \qquad \text{Eq 7}$$